DETAILED ACTION

1. This supplemental Office action corrects the error in the previous Office action of 11/16/2010, i.e., making the action final. In the advisory action mailed on 09/17/2010 the Examiner indicated that the amendments to the claims were not entered because they raised new issues and were not deemed to put the application in a better form for appeal by materially reducing or simplifying the issues for appeal. For these reasons, the action issued after the submission of a request for continued examination under 37 CFR 1.114 should not have been made final. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. The final action of 11/16/2010 is hereby vacated.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/28/2010 has been entered.

Claims 4, 5, 32, and 33 have been cancelled. Claims 19-29 and 34 have been withdrawn. Claims 1 and 12 have been amended.

Claims 1-3, 6-18, 30, and 31 are under examination.

3. All rejections pertaining to claims 4, 5, 32, and 33 are moot because the applicant cancelled the claims in the reply filed on 09/28/2010.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-3, 6-18, 30, and 31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6, 12-17 of U.S. Patent No. 6,268,119 in view of each Oka et al. (U.S. Patent No. 5,298,165, of record), Oka et al. (PGPUB 2004/0251195, of record), Fukuda et al. (WO 02/087660, Abstract, of record), and Rubinstein et al. (Proc. Natl. Acad. Sci. USA, 1995, 92: 10119-10112, of record).

The instant claims are drawn to a method of preparing a concentrate of nucleated cells by introducing a cell-containing solution which contains both nucleated cells and unnecessary cells into a filter device comprising an inlet and an outlet, wherein the filter device capture the nucleated cells and discharges the unnecessary cells, followed by the addition of a recovery solution to recover the nucleated cells captured by the filter; before being introduced into the filter device, the cell-containing solution is separated into a layer rich in nucleated cells, a nucleated cell-diluted layer (i.e., plasma), and a layer rich in unnecessary cells, wherein the layer rich in unnecessary cells is the first to be introduced into the filter device, followed by nucleated cell-diluted layer and the layer rich in nucleated cells in this order; the recovery solution could be the nucleated cell-diluted layer (i.e., plasma) and the recovery solution is further centrifuged to concentrate the nucleated cells (claims 1, 7-10, 30, and 31). Separation of the cell-containing solution into layers takes place by centrifugation or by agglutination with hydroxyethyl starch (HES) followed by centrifugation (claims 2, 3, and 6), the unnecessary cells are erythrocytes, and the nucleated cells are hematopoietic stem cells (claim 1). The filter device further contains an aggregate-capturing material between the inlet and the filter and a porous recovery solution-rectifying material between the filter and the outlet; the filter and the recovery solution-rectifying material form a porous filter material wherein the value obtained by dividing the effective filtration area of the filter material by the thickness of the nucleated cell-capturing filter is between 15 and 120 cm (claims 11-13). The filter material is non-woven fabric (having an average fiber diameter of 1.1-3.0 μm for the cell-capturing material or 0.5-1.5 μm for

the rectifying material, with a packaging density of 0.1-0.3 g/cm^3), a sponge-like structure (having an average pore diameter of 7-25 μm for the cell-capturing material or of 2-10 μm for the rectifying material, with a porosity between 55 and 90%), or a combination of a non-woven fabric with a sponge-like structure (claims 14-18).

The patent claims recite a cell separation method comprising introducing a fluid containing cells to be recovered and cells to be removed into a cell-capturing device having an inlet and an outlet and a cell-capturing means which captures the cells to be recovered and discharges the cells to be removed, followed by the introduction of a liquid into the cell-capturing means to recover the captured cells; the cell-capturing means comprises non-woven fabrics with a fiber diameter of 1.0-30 μm or porous spongy structure having a pore size of 2.0-25 μm (claims 1, 6, and 12). The cells to be recovered are nucleated cells such as hematopoietic stem cells and the cells to be removed are erythrocytes (claims 13-17). The specification defines that the liquid used to recover the captured cells could be plasma (p. 8, lines 21-51, p. 12, line 63 through lines 1-5 of p. 13). The patent claims do not recite a composite filter comprising an aggregate-capturing material, a nucleated cell-capturing material, and a recovery solution rectifying material, nor do they recite using centrifugation to separate the cell-containing solution into a layer rich in nucleated cells, a nucleated cell-diluted layer, and a layer rich in unnecessary cells before introducing it into the filter device or adding HES before centrifuging the cell-containing solution. However, at the time the invention was made, such limitations were well known and used in the prior art. For example, Oka et al. (U.S. Patent NO 5,298,165) teach improved leukocyte capturing by using a

composite filter comprising a pre-filter (i.e., an aggregate-capturing material), a nucleated cell-capturing filter, and a microfilter, in this order (Abstract, column 8, lines 25-45, column 10, lines 19-30 and 62-67, column 11, lines 1-16). It is noted that the instant specification defines the recovery solution rectifying material as a porous filter having a packing density of 0.1-0.3 g/cm^3 and an average fiber diameter of 0.5-1.5 μm (p. 19, second full paragraph). Since Oka et al. (U.S. Patent NO 5,298,165) teach their microfilter as having a packing density of 0.15-0.38 g/cm^3 and a fiber diameter of 0.5-1.4 μm (column 8, lines 60-66, column 12, lines 53-55), their microfilter has the same properties as the claimed recovery solution rectifying material, i.e., their microfilter is a recovery solution rectifying material. In addition, both Oka et al. (PGPUB 2004/0251195) and Fukuda et al. teach a method for isolating nucleated cell from blood, the method comprising centrifuging the blood, i.e., separating the blood into a buffy coat (layer rich in nucleated cells), plasma (nucleated cell-diluted layer), and an erythrocyte pellet (layer rich in unnecessary cells), followed by introducing the separated blood into a filter device, wherein such a separation results in high retention of nucleated cells on the filter (see Oka et al., p. 1, paragraphs 0005 and 0010; Fukuda et al., Abstract). Rubinstein et al. teach adding HES to blood to enhance erythrocyte sedimentation (p. 10120, column 2, third paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the patent claims by introducing the HES/centrifugation steps and using a composite filter as taught by the prior art, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because the art teaches that such modifications result in increased retention of

nucleated cells within the filter device. With respect to the different values recited in the instant claims 11, 12, 15, and 17, it would have been obvious to one of skill in the art to vary the parameters (i.e., fiber or pore size and packaging density) to optimize the results according to the nucleated cell to be separated. With respect to centrifuging the recovery solution, it would have been obvious to one of skill in the art to do such in order to further concentrate the recovered nucleated cells. With respect to using a combination between a non-woven and a sponge-like material, it would have been obvious to one of skill in the art to do so in order to improve the performance of the filter device. With respect to the limitation of the recovery solution being nucleated cell diluted layer (i.e., plasma, see above), since the specification defines that the recovery solution could plasma, it would have been obvious to one of skill in the art to use such a layer to achieve the predictable result of recovering the nucleated cells.

Thus, the instant claims and patent claims are obvious variants.

Applicant's arguments are not new and were previously addressed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3, 6-17, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sumita et al. (U.S. Patent No. 6,268,119, of record), in view of each Oka et al. (U.S. Patent No. 5,298,165, of record), Fukuda et al. (WO 02/087660, of record), Oka et al. (PGPUB 2004/0251195, of record), and Rubinstein et al. (Proc. Natl. Acad. Sci. USA, 1995, 92: 10119-10122, of record).

Sumita et al. teach a method of preparing a nucleated cell concentrate by introducing blood into a filter device comprising a filter material capable of capturing nucleated cells and discharging unnecessary cells, followed by the introduction of a recovery solution to elute the captured nucleated cells; the filter material could be a non-woven fabric with a diameter of 1-30 μm or a spongy structure with a pore size of 3-20 μm, the nucleated cells are hematopoietic stem cells, the unnecessary cells are erythrocytes, and the recovery solution could be plasma (claims 1 and 30) (column 2, lines 51-67, column 3, lines 1-8 and 50-55, column 5, lines 18-67, column 6, lines 27-60, column 8, lines 21-51, p. 12, line 63 through lines 1-5 of p. 13).

Sumita et al. do not teach a composite porous filter material comprising, in a direction from the inlet to the outlet, an aggregate-capturing material, a nucleated cell-capturing material, and a recovery solution-rectifying material, wherein the filter material comprises a non-woven fabric, a sponge-like structure, or a combination between a non-woven fabric and a sponge-like structure (claims 11-17). Oka et al. ('165) teach improved leukocyte capturing by using a porous composite filter made of a non-woven material comprising in the upstream to downstream order: a pre-filter (i.e., an aggregate-capturing material), a nucleated cell-capturing filter, and a microfilter

(Abstract, column 8, lines 25-45, column 10, lines 19-30 and 62-67, column 11, lines 1-16). The porous composite filter of Oka et al. (U.S. Patent No. 5,298,165) has an average fiber diameter of 1.0-2.0 μm for the nucleated cell-capturing material and of 0.5-1.4 μm for the microfilter material and a packing density of 0.15-0.38 g/cm^3 (column 8, lines 60-66, column 10, lines 19-30). With respect to the limitation of recovery solution rectifying material, it is noted that the instant specification defines the recovery solution rectifying material as a porous filter having a packing density of 0.1-0.3 g/cm^3 and an average fiber diameter of 0.5-1.5 μm (p. 19, second full paragraph). Since Oka et al. ('165) teach their microfilter as having a packing density of 0.15-0.38 g/cm^3 and a fiber diameter of 0.5-1.4 μm (column 8, lines 60-66, column 12, lines 53-55), their microfilter has the same properties as the claimed recovery solution rectifying material, i.e., their microfilter is a recovery solution rectifying material. Therefore, Oka et al. ('165) teach a porous composite filter comprising in a direction from the inlet to the outlet, an aggregate-capturing material, a nucleated cell-capturing material, and a recovery solution-rectifying material. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the filter device of Sumita et al., by using the composite filter device of Oka et al. ('165), with a reasonable expectation of success. The motivation to do so is provided by Oka et al. ('165), who teach that composite filters are very efficient in removing nucleated cells from blood. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that composite filters can be successfully used to capture blood nucleated cells. With respect to the limitations recited in claim 17, Oka et

al. ('165) teach an average pore diameter of 6-20 μm for the nucleated cell-capturing material, of 4-12 μm for the recovery solution-rectifying material and a packing density of 0.15-0.38 g/cm^3 (column 10, lines 41-45, column 12, lines 53-55). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the sponge-like filter of Sumita et al. according to the teachings of Oka et al. ('165) to achieve the predictable result of obtaining a composite sponge-like filter with improved properties.

Sumita et al. and Oka et al. ('165) do not teach using centrifugation to separate the cell-containing solution into a layer rich in nucleated cells, a nucleated cell-diluted layer, and a layer rich in unnecessary cells before introducing it into the filter device or adding HES before centrifuging the cell-containing solution (claims 1-3 and 6-8). However, at the time the invention was made, such limitations were well known and used in the prior art. For example, both Oka et al. (PGPUB) and Fukuda et al. teach a method for isolating nucleated cell from blood, the method comprising centrifuging the blood with the simultaneous introduction of the separated components into nucleated cell-capturing filters, wherein the method results in high retention of nucleated cells on the filter (see Oka et al., p. 1, paragraphs 0005 and 0010, p. 2, paragraph 0017; Fukuda et al., Abstract). Such a method would necessarily result in a cell gradient comprising a buffy coat at the top (layer rich in nucleated cells), plasma in the middle (nucleated cell-diluted layer), and an erythrocyte pellet at the bottom (layer rich in unnecessary cells) with the introduction into the filter of the separated components in the order of erythrocyte pellet first, plasma second, and buffy coat third (claims 1, 7, and 8). It would

have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Sumita et al. and Oka et al. ('165) by introducing into the filter device a blood cell gradient as taught by Fukuda et al. and Oka et al. (PGPUB), with a reasonable expectation of success. The motivation to do so is provided by Fukuda et al., who teach that such a method results in high retention of nucleated cells on the filter (Abstract). One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that such steps can be successfully used to obtain nucleated cells from blood. Sumita et al., Oka et al. ('165), Fukuda et al., and Oka et al. (PGPUB) do not teach using HES in combination with centrifugation (claims 3 and 6). Rubinstein et al. teach adding HES to blood to enhance erythrocyte sedimentation (p. 10120, column 2, third paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Sumita et al., Oka et al. ('165), Fukuda et al., and Oka et al. (PGPUB) by introducing the HES before the centrifugation step, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to improve separation of blood into its components. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that HES improves erythrocyte elimination. With respect to the limitation of the filter having value obtained by dividing the effective filtration area by the thickness of the nucleated cell-capturing material of 15-120 cm (claims 11 and 12) or of porosity of 55-90% (claim 17), it would have been obvious to one of skill in the art to use routine experimentation to vary these parameters to optimize the results according to the

nucleated cell to be separated (see Oka et al.'165, column 6, lines 3-9). With respect to centrifuging the recovery solution (claim 10), it would have been obvious to one of skill in the art to do such in order to further concentrate the recovered nucleated cells. With respect to the limitation of the recovery solution being nucleated cell diluted layer (claim 9), since Sumita et al. teach that plasma can be used s a recovery solution and since the nucleated cell diluted layer is plasma (see above), it would have been obvious to one of skill in the art to use such a layer to achieve the predictable result of recovering the nucleated cells. With respect to claim 30, it would have been obvious to one of skill in art, t the time the invention was made, to concentrate the cells by centrifugation because doing such was common practice in the art.

Thus, the claimed invention was *prima facie* obvious at the time it was made.

8. Claims 1-3, 6-18, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sumita et al. taken with each Oka et al. (5,298,165), Fukuda et al., Oka et al. (PGPUB 2004/0251195), and Rubinstein et al., in further view of Tanaka et al. (U.S. Patent No. 6,048,464, of record).

The teachings of Sumita et al., Oka et al. (U.S. Patent NO 5,298,165), Fukuda et al., Oka et al. (PGPUB 2004/0251195), and Rubinstein et al. are applied as above for claims 1-3, 6-17, 30, and 31. Sumita et al., Oka et al. (U.S. Patent NO 5,298,165), Fukuda et al., Oka et al. (PGPUB 2004/0251195), and Rubinstein et al. do not teach a filter made from a combination of non-woven fabric with a sponge-like structure (claim 18). However, at the time the invention was made, such combination filters were taught

by the prior art. For example, Tanaka et al. teach a nucleated cell-capturing filter comprising both a sponge-like structure and a non-woven fabric (Abstract, column 3, lines 19-46, column 6, lines 17-26). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Sumita et al., Oka et al. (U.S. Patent NO 5,298,165), Fukuda et al., Oka et al. (PGPUB 2004/0251195), and Rubinstein et al. by using a combination filter comprising both a sponge-like structure and a non-woven fabric to achieve the predictable result of capturing nucleated cells.

Thus, the claimed invention was *prima facie* obvious at the time it was made.

The applicant argues that the examiner has misinterpreted the claims. This is not found persuasive because plasma is the nucleated cell diluted layer. Thus, similar to the instant claims, the combination of the cited art teaches introducing in order: the unecessary cells, the nucleated cell-diluted layer, and the layer rich in nucleated cells. The argument of unexpected results is not found persuasive because separation by first introducing the layer rich in unecesary cells folowed by the layer rich in nucleated cells was already taught by both Oka (PGPUB) and Fukuda. The applicant argues that Oka (PGPUB) and Fukuda are both related to removing and not to the recovery of the nucleated cells. This is not found persuasive. Both Oka (PGPUB) and Fukuda teach their method (i.e., first introducing the layer rich in unecesary cells followed by the layer rich in nucleated cells) as very efficient in retaining the nucleated cells on the filter. Thus, one of skill in the art separation of nucleated cells from erythocytes. as being very efficient. Thus, onr of skill in the art seeking to isolate leukocyte would have known that modifyiying the method of Oka ('165) by first introducing the layer rich in unecesary

cells followed by the layer rich in nucleated cells would improve the leukocyte yield. For the same resons, the argument of unexpected results is not found persuasive.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/

Primary Examiner, Art Unit 1633